LINKER CONTAINING ARYLNITRO, ANTIBODY-DRUG CONJUGATE CONTAINING LINKER AND USE OF LINKER

[0001] The present application is based on and claims the benefit of priority from Chinese application No. 201811002559.2, filed on Aug. 30, 2018, the disclosures of which are incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] The present application belongs to the field of medicinal chemistry, specifically relates to a linker containing arylnitro, an antibody-drug conjugate containing the linker and use of the linker, as well as a pharmaceutical composition comprising the antibody-drug conjugate and use of the antibody-drug conjugate for treatment and/or prevention of a disease.

BACKGROUND ART

[0003] An antibody-drug conjugate (ADC) organically combines a monoclonal antibody with a cytotoxin, thereby combines the advantages of both antibody and cytotoxic drug and has characteristics such as strong targeting, high cytotoxicity, low toxic and side effect, long degradation half-life. ADC structurally comprises three components: an antibody, a small molecule cytotoxin and a linker, in which the role of antibody is to achieve targeting, the role of cytotoxin is to kill target cells, and the role of linker is to realize the organic combination of antibody and cytotoxin in structure so as to form an organic entirety. The design of linker is of great significance to ADC drugs. As a junction and bridge connecting the monoclonal antibody and the small molecule cytotoxin, the linker has a nature that directly affects the efficacy and safety of ADC. As the linker of ADC, it must make the drug stable in the blood circulation system and release the active toxin quickly and effectively after reaching the target tissue. The construction of linkers has become a core element and a major challenge restricting the development of ADCs.

[0004] Regarding the development of ADC linkers, there are many important considerations, including the coupling site of antibody, the average number of cytotoxins linked to each antibody molecule (drug to antibody ratio, DAR), the cleavability of linker, the hydrophilicity of linker, etc. The linker should have a long-term stability in the circulatory system, and can release cytotoxin quickly and effectively after reaching the target cells, so as to exert the two advantages of antibody targeting and high toxin efficiency. At the present stage, the design idea of linker is mainly to utilize the difference between tumor cells and blood circulation system environment to achieve selective release of toxin in tumor tissues.

[0005] According to the different cleavage modes to release toxins, the linkers can be divided into two categories: cleavable linkers and non-cleavable linkers. Regarding the ADCs containing cleavable linkers, after being degraded in target cells, they can release the free parent toxin itself to exert its effectiveness, while regarding the ADCs containing non-cleavable linkers, after they are degraded in target cells, the active substance exerting effectiveness is often not the cytotoxin itself, but a complex formed by the toxin and the amino acid residue at the linker-antibody coupling site.

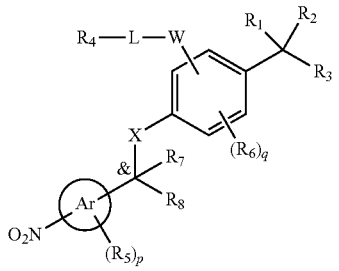
[0006] According to the different cleavage mechanisms, the cleavable linkers are classified into chemically cleavable linkers and enzymatically cleavable linkers. The enzymatically cleavable linkers have significant advantages over the chemically cleavable linkers in terms of stability and drug release selectivity. At the present stage, the enzymatically cleavable linkers have become the mainstream choice for ADCs. The relatively mature enzymatically cleavable linkers studied are dipeptide linkers whose cleavage depends on cathepsin B.

[0007] The existing ADC drug-releasing enzymes such as cathepsin B or β-glucuronidase are non-tumor specific enzymes, which are widely present in the lysosomes of most cells of mammal. For those unavoidable off-target ADCs, they can be degraded by the drug-releasing enzymes in the lysosomes of normal tissues and release highly lethal cytotoxin drugs such as MMAE, which are toxic to normal tissues, and the non-ionic free cytotoxins can further penetrate the normal cell membrane usually via the bystander effect to cause systemic toxicity to surrounding tissues.

[0008] For the current mainstream enzymatically cleavable ADCs, the lack of tumor specificity and the off-target toxicity caused by non-specific enzymolysis are common problems during drug release process.

Contents of the Disclosure

[0009] The present application relates to a compound represented by Formula I or a salt thereof,



I

[0010] wherein:

[0011] R_1 is hydrogen, methyl, ethyl, n-propyl or isopropyl;

[0012] R_2 is hydrogen, methyl, ethyl, n-propyl or isopropyl;

[0013] R_3 is fluorine, chlorine, bromine, iodine or